REMARKS

Claims 1-11 and 28-47 were pending. The specification has been amended to comply with 37 CFR §1.78(a)(2) and (a)(5). Claims 1, 7, 28, 32, 37, and 43 have been amended to recite a SEQ ID NO. and to correct a problem with a term not having antecedent basis. Upon entry of this amendment claims 1-11 and 28-47 will be pending.

No new matter has been added.

Priority

The Office alleges that Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C § 120. Applicants have amended the specification so that the relationship of the priority application is specified. Applicants have moved the related applications to the "Background of the Invention" section of the present application, thereby rendering the objection moot.

Rejections under 35 U.S.C. § 112

Claims 1-11 and 28-47 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Office alleges that the claims are vague and indefinite because there "are multiple sequences for HIV Vpr with minor differences in the chemical structure...and the claims do not refer to a particular sequence identifier, it is unclear which sequence the claims encompass, and thus the meets and bounds of the claims are unclear." (Office Action, page 3) Applicants respectfully disagree.

Although, one of ordinary skill in the art would understand what is described in the pending claims, Applicants have amended to the claims to include a particular sequence identifier. However, the inclusion of the sequence identifier, should not be construed as to limit the present application to the Vpr sequence described. One of skill in the art would be able to routinely and without an undue burden be able to use a Vpr fragment that comprises conservative substitutions and performs the same function as that as described in the present invention and claims.

Claims 29-31 also stand rejected for alleged insufficient antecedent basis for the limitation "said nucleic acid molecule." Applicants have amended claim 28 to include the element "nucleic acid molecule" rendering this rejection moot.

In view of the foregoing, Applicants respectfully request that the rejections under 35 U.S.C. § 112 be withdrawn.

In view of the foregoing, Applicants respectfully request that rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 1 and 7-9 remain rejected under 35 U.S.C § 102(e) as allegedly anticipated by Cohen *et al.* (U.S. Patent No. 6,043,081, hereinafter the "Cohen reference"). The Office considered Applicants' arguments but found them not to be persuasive. According to the Office this is because

> Even though Cohen *et al.* do not use the term conjugated composition, they do teach different forms of conjugated composition including a chimeric peptide, a nucleic acid encoding the chimeric peptide, and a nucleic acid Vpr-fragment. For example, they teach, "The term therapeutic agent should be taken in a broad sense so as to also include a combination of at least two such therapeutic agents. Further, the DNA segments or proteins according to"...They also recite, "The anti-viral treatment can be effected through transfections of a patient's hematopoietic cells with a DNA construct harboring a VPR/VPX chimeric protein and followed by readministration of the transfected cells." Therefore, the rejection stands.

(Office Action, page 4). Applicants respectfully disagree.

The standard for anticipation is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984).

The Cohen reference fails to discuss or even suggest each and every limitation of claims 1 and 7-9. Applicants respectfully disagree with the Office's interpretation of the Cohen reference. The Cohen reference ***does not*** discuss a conjugated composition as it is used in the pending claims. The Office refers to the quotes used above as support that the

Cohen reference does discuss a conjugated composition, even though as the Office readily admits, it does not use the terms or anything like the term "conjugated composition." Instead the Cohen references states that a therapeutic agent should be taken to include "at least two such therapeutic agents." This is vastly different than a conjugated composition that under the definition used by the Cohen reference would only be considered ***a single*** therapeutic agent. Administering two agents as a combined therapeutic agent does not make the two agents conjugated to one another. Conjugation means that the components are attached to one another through an interaction (*i.e.* covalent or ionic bond).

The Office cites the Cohen statement of a "DNA construct harboring a VPR/VPX chimeric protein" as evidence that it discusses a conjugated composition. However, the construct that Cohen is referring to is a DNA construct encoding a protein that contains amino acids derived from Vpr and Vpx. The chimeric Vpr/Vpx construct is either completely DNA or completely protein, not a combination or conjugation of DNA and protein. None of the examples or detailed description of the Cohen reference refer to or describe a composition that comprises a protein conjugated to a nucleic acid molecule. Therefore, The Cohen reference fails to anticipate the present invention.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) be withdrawn.

Claim 1 and 5-11 remain rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO9608970 (hereinafter the "'970 reference"). The Office argues that because the present specification defines a fragment of Vpr protein as a protein that is not complete and that the specification states, "For example, a protein having amino acids 1-95 of Vpr protein, but which is missing amino acid 96...is a fragment of Vpr protein." (Office Action, page 5). And that the '970 reference teaches that fragments are more than 5 amino acids in length "derived from Vpr" also define a functional fragment as a fragment that "retains its ability to inhibit cell proliferation and/or induce differentiation of undifferentiated cells and/or prevent lymphocyte activation." (Office Action, page 5). Therefore, the Office reasons that since the Vpr fragment is "encompassed by the teaching of WO9608970, which fragment always and absolutely comprises amino acid

sequence 17-36 and/or 59-84. As long as one fragments [sic] comprises the recited fragments, the cited art anticipate [sic] the instant claims." (*Id.*) Applicants respectfully disagree.

Applicants respectfully assert that the Office's argument is contrary to law and the rules of the M.P.E.P. If one were to use the Office's reasoning a species would never be patentable once a genus has been described because, by definition, the genus would always and necessarily contain one of the species. However, it is well accepted that a species is patentable even if a genus containing the species has already been described (see, for example, M.P.E.P. § 2131.02). For the '970 reference to anticipate the present application, one of skill in the art would have to able to "at once envisage" the specific compound(s) of the present invention within the generic formula of the '970 reference, for the present invention to be anticipated. (*Id.*). One of skill in the art would not be able to instantly envisage fragments of Vpr that comprise amino acid sequence 17-36 and/or 59-84. Using the '970 reference as a start one of skill in the art would only know that fragments need to contain at least 5 amino acids and be functional. However, there is no indication that the fragment would always and necessarily have to contain amino acid sequence 17-36 and/or 59-84. The '970 reference does not clearly name a species of Vpr fragments that contains amino acid sequence 17-36 and/or 59-84. As the court has stated "The fact that a claimed compound may be encompassed by a disclosed generic formula does not itself render the compound obvious" or in this case anticipated. (*In re Brian Baird*, 16 F.3d 380) Since the '970 reference would not lead one of skill in the art to have "at once envisaged" present invention, the '970 reference fails to anticipate it.

Thus, in view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-7, 10, and 11 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over the Cohen reference in view of Katz *et al.* (U.S. Patent No. 6,005,004, hereinafter the "Katz reference") and Zuckermann *et al* (U.S. Patent No. 6,468,986, hereinafter the "Zuckermann reference."). Applicants respectfully disagree.

The Office states as to motivation the "Cohen reference...teach[es] conjugating Vpr with a nucleic acid construct as discussed above." (Office Action, page 7). As Applicants noted above the Cohen references ***does not*** discuss "conjugating Vpr with a nucleic acid construct." At most the Cohen reference discusses a chimeric protein comprising Vpr protein with another protein that is encoded by a nucleic acid molecule. Therefore, the Cohen reference fails to discuss any conjugated composition and more of more relevance Applicants conjugated composition.

Furthermore, neither the Katz reference nor the Zuckermann reference discuss Vpr, fragments of Vpr, or conjugating Vpr with a nucleic acid molecule. One of skill in the art would not have been motivated to combine the three references because not only do the references not cite one another either explicitly or implicitly, but there is no suggestion within the references as to why one would modify the Cohen reference to create Applicants' invention. There are thousands of references available in the prior art from which to choose from and it is only based on Applicants' disclosure that the Office was able to pick and choose references to come up with the alleged combination. In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would **impel** one skilled in the art to do what the patent applicant has done. (citations omitted; emphasis added)

Significantly, the Office Action identifies no "motivating force" that would "impel" persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention.

In addition, it appears that the only motivation that the Office is using to combine the references is the use of the Applicants' specification and hindsight

reconstruction, which is strictly forbidden. *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."). When assessing whether or not a combination of references would have produced a claimed invention, one must consider the teaching of each reference as a whole without undue emphasis on those features that would support a finding of obviousness. *In re Wesslau*, 147 U.S.P.Q. 391 (C.C.P.A. 1965) (it is impermissible to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the references fairly suggest to one of ordinary skill in the art).

Consideration of the cited references as a whole for what they each fairly suggest, demonstrates that a person of ordinary skill seeking to combine them would not have produced any claimed invention. In this respect, the Office Action has apparently picked one particular element from Cohen, one particular element from Katz, and one particular element from Zuckermann. One skilled in the art, however, would ***not*** be motivated to pick and choose only those specific elements referred to in the Office Action from the many elements recited in the references and combine the selected elements in the specific manner indicated in the Office Action. For example, one skilled in the art would not have picked only the polycationic amino acid sequence from reading the Katz reference because if taken in its entirety one skilled in the art would have taken a composition of an omega-3 fatty acid ***and*** a polycationic amino acid sequence, which contains elements not recited in the present invention. A person of ordinary skill in the art would not expect the composition disclosed in the Katz reference to work without the omega-3 fatty acid and therefore any composition taken from Katz would include the omega-3 fatty acid. Zuckermann does not discuss using a polycationic amino acid sequence with a conjugated composition as is claimed in the present application and therefore there would have been no expectation of success of using polycationic amino acid sequences with a conjugated composition because of the focus in these references on the delivery of polynucleotides into a cell.

Indeed, it appears that the only guide to picking and choosing particular elements from the cited art of records appears to have been the present application. Thus, the combination of references is improper for, at the very least, failure to provide motivation

to combine references and for its use of hindsight reconstruction based upon Applicants' disclosure. Furthermore, as discussed above the references either alone or in combination do not suggest or motivate a person of ordinary skill in the art to use the fragments recited in the pending claims.

Thus, because the Cohen reference does not teach a conjugated composition and one of skill in the art would not have been motivated to combine and/or modify the cited references to produce Applicants' invention, the present invention is not obvious.

Claims 1-4 also stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over the '970 reference in further view of the Katz reference and the Zuckermann reference. Applicants respectfully disagree.

As discussed above the specification of the '970 reference does not discuss or suggest the conjugated compositions of the present invention. At most the '970 reference provides an "obvious to try" motivation, but this has been repeatedly struck down by the court as a reason for rejecting a claim as being obvious over the prior art. As the court has stated:

> An invention is "obvious to try" "where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful.

(*Merck v. Biocraft*, 874 F.2d 804). None of the references, either alone or in combination, give "direction" as to the possible fragments of Vpr that would be part of the present invention. Without this necessary "direction" the references fail to provide the requisite motivation that would ***impel*** one of skill in the art to combine and/or modify the references to create the present invention. As previously stated, it appears that the Office has selectively picked and chosen elements from all three references without using the references for what they fairly suggest. If one of skill in the art would have read the three references for what they fairly suggest the skilled artisan would not have been motivated to combine the references.

Additionally, the selection of the fragments contain amino acid sequence 17-36 and/or 59-84 is not obvious from the teachings of the references and was not known until the Applicants invention. Numerous fragments could have been chosen from the Vpr

protein sequence and the fragments would not have had the residues recited and/or facilitated the translocation of moieties (e.g. nucleic acid molecules and therapeutic compounds) to the nucleus.

As stated in Applicants previous response, Applicants invention of defining the fragments on Vpr that can be used for nuclear localization and conjugating the fragments to either a nucleic acid molecule or a therapeutic compound was unexpected. These results are described in the present application (see, for example, pages 36-37). The present application states:

> Previously it has been shown that Vpr localizes in the nucleus of infected and transfected cells in the absence of other viral proteins despite the lack of a canonical nuclear localization signal

(Specification, page 37, lines 1-3). Since, there was no clear understanding how Vpr was transported into the nucleus it could have been possible that Vpr did not contain a nuclear localization fragment(s) within the protein itself. It is only through the present invention that these fragments were identified. There are no teachings within the references cited by the Office, either alone or in combination, that discuss mutating the residues within these fragments to inhibit nuclear localization of Vpr and therefore, could be identified as being able to be used as a nuclear transport signal when conjugated to a nucleic acid molecule. Therefore, the result of defining and identifying two nuclear localization fragments within Vpr ***was unexpected***. Accordingly, the pending claims are ***not*** obvious.

Thus, in view of the foregoing, Applicant respectfully submits that the Office has failed to establish a *prima facie* case of obviousness. In particular, the Office has failed to provide any motivation that would *impel* one skilled in the art to modify and/or combine the cited references so as to produce Applicants' claimed inventions. The present invention has also unexpectedly determined the fragments of Vpr that can be used as nuclear localization fragments when conjugated to a nucleic acid molecule.

In view of the foregoing, Applicants respectfully request the rejection under 35 U.S.C. § 103(a) be withdrawn.

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Conclusion

Applicant believes the claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicant invites the Examiner to contact the undersigned at (215) 665-6928 to clarify any unresolved issues raised by this response.

Respectfully submitted,

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